LABOPHARM AND PURDUE PARTNER ON ONCE-DAILY TRAMADOL

A definitive licensing and distribution agreement has been made between Labopharm Inc. and Purdue Pharma LP for the once-daily formulation of tramadol. Labopharm is actively seeking commercialization of the analgesic, and has completed two Phase III clinical studies in the United States, with a third already in progress. It is anticipated that a New Drug Application will be submitted to the US Food and Drug Administration before the end of 2005. Tramadol is currently available in the United States only in immediate-release form, which requires four to six doses per day for analgesic maintenance. Labopharm is based in Quebec, Canada; Purdue is based in Stamford, Connecticut. (Source: Purdue Pharma press release, August 15, 2005.)

NEW STUDY RESULTS FOR EXTENDED-RELEASE OXYMORPHONE

In a Phase III trial conducted under the special protocol assessment process of the US Food and Drug Administration (FDA), extended-release oxymorphone (Endo Pharmaceuticals, Chadds Ford, PA) was shown to make a statistically significant ($p < 0.0001$) difference in pain scores, as compared with placebo. The trial, lasting 12 weeks, involved 205 opioid-naïve patients with moderate to severe low back pain.

Extended-release oxymorphone was initially approved by the FDA on October 20, 2003. However, the FDA made the approval with the condition that Endo provide additional clarification and information, in addition to a trial confirming the safety and efficacy of the product beyond what had already been demonstrated. This supplemental study will be part of the response submitted to the FDA by Endo, anticipated to be finished in early 2006. (Source: Endo Pharmaceuticals press release, August 22, 2005.)

ONLINE PHARMACY OWNER INDICTED

Christopher William Smith, 25, owner and operator of Xpress Pharmacy Direct, was arrested at his home in Prior Lake, MN this week. Dr. Philip Mach, of Franklin Park, NJ, and Bruce Jordan Lieberman, 45, of Farmingdale, NY, were also charged in a multiple-count federal indictment. The indictment features more than a dozen charges related to the operation of Smith's online business. Smith was ordered held without bond; his attorney, Joe Friedberg, would not comment.

The grand jury alleged that Smith provided prescription drugs without verifying customer prescriptions. Orders were obtained through spam e-mails, Internet sites, and telemarketing. Smith is considered one of the world's worst spammers, according to the Spamhaus Project, an international antispam organization based in the United Kingdom.

The indictment includes counts of conspiracy to dispense controlled substances, wire fraud, money laundering, distribution of controlled substances, and introducing of misbranded drugs into interstate commerce. It also claims that from March 2004 to May 2005, Xpress Pharmacy Direct generated sales of more than $20 million from medications containing hydrocodone. In May 2005, a federal judge shut down the business and appointed a receiver to take control of the assets. Federal authorities seized $1.8 million in luxury cars, two homes, and $1.3 million in cash.

Prosecutors allege that Smith had Dr. Mach issue approximately 72,000 prescriptions from July 2004 to about May 2005. Dr. Mach is registered to practice medicine in New Jersey, but allegedly wrote prescriptions for patients throughout the United States without having any contact with them or their primary care physicians.

The US Attorney's Office said that Mach was represented by Bruce Levy of New Jersey. A call to his office was not immediately returned.

Smith's former accountant, Bruce Lieberman, was accused of helping Smith hide the origin of money earned from the prescription drug business. He also allegedly helped Smith process credit cards. Marvin Zevin, Lieberman's attorney, declined to comment until his client had made his first court appearance. (Source: *Houston Chronicle*, August 25, 2005.)

THE BRAIN AND PLACEBO EFFECT

A new brain-imaging study published in the *Journal of Neuroscience* suggests that just thinking you are receiving treatment is enough to make you feel better. This phenomenon, known as the placebo effect, involves release of endorphins, the body's natural painkillers.

Previous studies showed general changes in brain activity associated with the placebo effect by using functional magnetic resonance imaging, and scientists therefore

hypothesized that the brain's opioid system was involved. The new study uses positron emission tomography (PET) brain scans, and the researchers were able to focus on a specific type of brain receptor and track its response to a placebo.

The PET scans used by Jon-Kar Zubieta of the University of Michigan and his colleagues measured the activity of mu opioid receptors, an integral part of the body's natural painkilling system. The receptors help transmit pain signals from one nerve cell to the next. In a randomized trial, 14 healthy male volunteers were asked to undergo the slightly painful but harmless procedure of having salt water injected into their jaws. For the next 20 minutes, volunteers documented the intensity of participants' pain every 15 seconds and then summarized the experience afterward. Some subjects received analgesic medication, whereas others were told they were being given medication but actually received none.

All participants who were told to expect medicine but given the placebo instead showed an increase in the activity of their endorphin system. Four brain regions were involved, and activity in specific areas was also associated with the subjects' own descriptions of pain. As an example, dorsolateral prefrontal cortex activity correlated to the effectiveness the volunteers anticipated from the "pain medicine."

The results from this study offer the first direct evidence that endorphins can help explain the placebo effect. "This deals a serious blow to the idea that the placebo effect is a purely psychological, not physical, phenomenon," Zubieta says. "We were able to see that the endorphin system was activated in pain-related areas of the brain, and that activity increased when someone was told they were receiving a medicine to ease their pain." It was noted, however, that the results may not apply to all groups; further investigation is needed to determine variations based on age, gender, and confounding factors such as illness. (Source: *http://www.scientificamerican.com*, August 24, 2005.)

HIGH RISK IN ULTRA-RAPID DETOXIFICATION

Online advertisements for pain-free anesthesia-based withdrawal from heroin and prescription painkillers are misleading and the actual technique is life threatening, according to a study appearing in the August 24, 2005, issue of the *Journal of the American Medical Association.*

The study of 106 patients, the most rigorous to date on the method, showed that patient withdrawal was as severe as those of addicts undergoing various other detoxification approaches. It was not pain free, and had no distinct advantage over other methods.

"Anyone who tells you it's painless can only honestly be referring to the period the person is under anesthesia," said coauthor Dr. Eric Collins of Columbia University Medical Center.

Study participants, all addicted to heroin, were divided into three treatment groups. Those receiving ultra-rapid detoxification were anesthetized for approximately four hours while receiving a large dose of a drug that blocks the brain's opioid receptors. The anesthesia is meant to mask the symptoms that would normally occur in an awake patient.

Patients still underwent withdrawal on awakening, despite being given additional medications for withdrawal symptoms that included anxiety, insomnia, achy muscles and joints, diarrhea, and vomiting. In addition, 80 percent of the anesthesia patients dropped out of followup treatment, a rate slightly higher than for another method in the study.

Since its introduction approximately 15 years ago, ultra-rapid detoxification has been linked with several deaths. In one case, New Jersey regulators fined and gave two-year license suspensions to two doctors practicing the method, although the doctors were cleared of negligence in seven deaths.

"Some doctors have put their financial interests way ahead of the well-being of their patients," said Dr. Thomas Kosten, professor of psychiatry at Yale University School of Medicine. He recommends maintenance with methadone or buprenorphine, instead of detoxification, for narcotics addiction. Methadone and buprenorphine create physical dependence themselves, however, and must be tapered gradually to avoid withdrawal or else continued indefinitely.

Some people choose detoxification because they do not want to exchange one drug for another, said Jake Epperly, who runs ultra-rapid detoxification programs in Chicago and Los Angeles. His company, Midwest Rapid Opiate Detoxification Specialists, treats approximately 250 addicts annually at $9,200 each.

"We've had no problems," Epperly said, adding that the study mentioned here used a different ultra-rapid method than the one in his programs.

The American Society of Addiction Medicine's policy statement on ultra-rapid detoxification says the method should be paired with counseling services and should be done only by trained staff with access to emergency medical equipment. In addition, patients should be informed of risks and benefits of the method compared with other options. (Source: Associated Press, August 24, 2005.)

METHYLNALTREXONE AND OPIOID-INDUCED CONSTIPATION

Progenics Pharmaceuticals, Inc., has announced additional positive data from a previously completed Phase III clinical trial of methylnaltrexone (MNTX) for the treatment of opioid-induced constipation in patients with advanced medical illness. Final data analysis of the MNTX 301 study showed significant improvements in measures

of constipation distress, bowel movement difficulty, and consistency, and global impressions of clinical change. No increases occurred in pain scores or opioid withdrawal symptoms in any treatment group. At both doses of MNTX that were tested, all prospectively defined secondary endpoints exhibited statistically significant differences compared to placebo. The findings will be presented at the International Association for the Study of Pain, 11th World Congress on Pain in Sydney, Australia.

In March 2005, Progenics announced positive top-line results from the MNTX 301 study. The primary efficacy endpoint, laxation within four hours, was highly statistically significant at both MNTX doses that were tested. In addition, statistically significant results were reported for both MNTX doses for two secondary endpoints, laxation within 24 hours and median time to laxation. In the study, 154 patients were randomized to receive one of three blinded single doses of study medication: placebo, MNTX 0.15 mg per kg, or MNTX 0.30 mg per kg. The MNTX doses were generally well tolerated in patients with advanced medical illness. In addition, there were no meaningful changes in pain levels or opioid withdrawal symptoms at four or 24 hours after double-blind dosing in any treatment group.

MNTX represents a broad treatment platform, and Progenics has ongoing clinical programs using three dosage forms. Subcutaneous MNTX is the subject of a second Phase III clinical trial (MNTX 302) in opioid-induced constipation in patients with advanced medical illness. Intravenous MNTX has successfully completed a Phase II trial for treatment of postoperative bowel dysfunction. Finally, oral MNTX has successfully completed two Phase I studies in healthy volunteers. (Source: Progenics Web site, *http://www.progenics.com*, August 22, 2005.)